FORM PTO-1390 (REV 11-2000)	U.S DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	ATTORNEY'S DOCKET NUMBER 3911-7
TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371		U S APPLICATION NO. (If known, see 37 C.F.R. 1.5) 09/856704 Unassigned
INTERNATIONAL APPLICATION NO. **PCT/NZ99/00198**	INTERNATIONAL FILING DATE **26 November 1999**	PRIORITY DATE CLAIMED **26 November 1998**

TITLE OF INVENTION

TREATMENT OF HYPERTENSION

APPLICANT(S) FOR DO/EO/US

VICKERS et al

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This is an express request to begin national examination procedures (35 U.S.C. 371(f). The submission must include items (5), (6), (9) and (21) indicated below.
4. ☒ The U.S. has been elected by the expiration of 19 months from the priority date (Article 31).
5. A copy of the International Application as filed (35 U.S.C. 371(c)(2)).
   - a. ☒ is attached hereto (required only if not communicated by the International Bureau).
   - b. ☐ has been communicated by the International Bureau.
   - c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
   - a. ☐ is attached hereto.
   - b. ☐ has been previously submitted under 35 U.S.C. 154(d)(4).
7. ☐ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   - a. ☐ are attached hereto (required only if not communicated by the International Bureau).
   - b. ☐ have been communicated by the International Bureau.
   - c. ☐ have not been made; however, the time limit for making such amendments has **NOT** expired.
   - d. ☐ have not been made and will not be made.
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☐ A English language translation of the annexes of the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11 To 20 below concern document(s) or information included:

11. ☒ An Information Disclosure Statement under 37 C.F.R. 1.97 and 1.98.
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 C.F.R. 3.28 and 3.31 is included.
13. ☒ A FIRST preliminary amendment.
14. ☐ A SECOND or SUBSEQUENT preliminary amendment.
15. ☐ A substitute specification.
16. ☐ A change of power of attorney and/or address letter.
17. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821-1.825.
18. ☐ A second copy of the published international application under 35 U.S.C. 154(d)(4).
19. ☐ A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
20. ☐ Other items or information.

JC18 Rec'd PCT/PTO 25 MAY 2001

U.S. APPLICATION NO. (if known, see 37 C.F.R. 1.5)	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
09/856704 Unassigned	PCT/NZ99/00198	3911-7

21. ☒ The following fees are submitted:

	CALCULATIONS	PTO USE ONLY

BASIC NATIONAL FEE (37 C.F.R. 1.492(a)(1)-(5):

-- Neither international preliminary examination fee (37 C.F.R. 1.482) nor international search fee (37 C.F.R. 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO $1000.00

-- International preliminary examination fee (37 C.F.R. 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO $860.00

-- International preliminary examination fee (37 C.F.R. 1.482) not paid to USPTO but international search fee (37 C.F.R. 1.445(a)(2)) paid to USPTO $710.00

-- International preliminary examination fee (37 C.F.R. 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4) $690.00

-- International preliminary examination fee (37 C.F.R. 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4) $100.00

ENTER APPROPRIATE BASIC FEE AMOUNT =						$	1000.00
Surcharge of $130.00 for furnishing the oath or declaration later than ☐ 20 ☒ 30 months from the earliest claimed priority date (37 C.F.R. 1.492(e)).						$	130.00
CLAIMS	NUMBER FILED		NUMBER EXTRA	RATE			
Total Claims	19	-20 =	0	X	$18.00	$	0.00
Independent Claims	5	-3 =	2	X	$80.00		160.00
MULTIPLE DEPENDENT CLAIMS(S) (if applicable)					$270.00	$	0.00
TOTAL OF ABOVE CALCULATIONS =						$	**1290.00**
☐ Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by 1/2.							0.00
SUBTOTAL =						$	**1290.00**
Processing fee of $130.00, for furnishing the English Translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 C.F.R. 1.492(f)). +							0.00
TOTAL NATIONAL FEE =						$	**1290.00**
Fee for recording the enclosed assignment (37 C.F.R. 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 C.F.R. 3.28, 3.31). **$40.00** per property +						$	0.00
Fee for Petition to Revive Unintentionally Abandoned Application ($1240.00 – Small Entity = $620.00)						$	0.00
TOTAL FEES ENCLOSED =						$	**1290.00**
						Amount to be: refunded	$
						Charged	$

a. ☒ A check in the amount of $1290.00 to cover the above fees is enclosed.
b. ☐ Please charge my Deposit Account No. 14-1140 in the amount of $_____ to cover the above fees. A duplicate copy of this form is enclosed.
c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 14-1140. A duplicate copy of this form is enclosed.
d. ☒ The entire content of the foreign application(s), referred to in this application is/are hereby incorporated by reference in this application.

NOTE: Where an appropriate time limit under 37 C.F.R. 1.494 or 1.495 has not been met, a petition to revive (37 C.F.R. 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

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29,009 May 25, 2001
REGISTRATION NUMBER Date

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of

VICKERS et al

Serial No. Unassigned

Filed: May 25, 2001

For: TREATMENT OF HYPERTENSION

Atty. Ref.: 3911-7

Group:

Examiner:

* * * * * * * * * * *

May 25, 2001

Assistant Commissioner for Patents
Washington, DC 20231

Sir:

PRELIMINARY AMENDMENT

Please amend the above application as follows:

IN THE CLAIMS

Please substitute the following amended claims for corresponding claims previously presented. A copy of the amended claims showing current revisions is attached.

3. (Amended) A method has claimed in claim 1 wherein the mammal has experienced an adverse postnatal environment comprising a hypocaloric or hypercaloric diet.

4. (Amended) A method as claimed in claim 1 wherein the mammal is an adult mammal.

7. (Amended) A method as claimed in claim 1 wherein the agent is administered to the mammal in combination with a second anti-hypertensive agent.

10. (Amended) A method as claimed in claim 8 wherein the effective concentration of the growth hormone, an analog thereof or a functionally equivalent ligand is increased through administration of an agent which either stimulates production of growth hormone or which lessens or prevents inhibition of growth hormone activity.

11. (Amended) A method as claimed in claim 8 wherein the effective concentration of growth hormone is increased through direct administration of growth hormone.

15. (Amended) The use as claimed in claim 13 wherein the medicament is for treating an adult human.

16. (Amended) The use as claimed in claim 13 wherein the agent is growth hormone.

17. (Amended) The use as claimed in claim 13 wherein the medicament is for administration in combination with a second anti-hypertensive agent.

REMARKS

The above amendments have been made to place the application in a more traditional format.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached pages are captioned "**Version With Markings To Show Changes Made**."

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS

3. (Amended) A method has claimed in [either claim 1 or claim 2] claim 1 wherein the mammal has experienced an adverse postnatal environment comprising a hypocaloric or hypercaloric diet.

4. (Amended) A method as claimed in [any one of claims 1 to 3] claim 1 wherein the mammal is an adult mammal.

7. (Amended) A method as claimed in [any one of the preceding claims] claim 1 wherein the agent is administered to the mammal in combination with a second anti-hypertensive agent.

10. (Amended) A method as claimed in claim 8 [or claim 9] wherein the effective concentration of the growth hormone, an analog thereof or a functionally equivalent ligand is increased through administration of an agent which either stimulates production of growth hormone or which lessens or prevents inhibition of growth hormone activity.

11. (Amended) A method as claimed in [either] claim 8 [or claim 9] wherein the effective concentration of growth hormone is increased through direct administration of growth hormone.

15. (Amended) The use as claimed in [either] claim 13 [or claim 14] wherein the medicament is for treating an adult human.

16. (Amended) The use as claimed in [any one of claims 13 to 15] claim 13 wherein the agent is growth hormone.

17. (Amended) The use as claimed in [any one of claims 13 to 16] claim 13 wherein the medicament is for administration in combination with a second anti-hypertensive agent.

TREATMENT OF HYPERTENSION

FIELD OF THE INVENTION

This invention relates to the treatment of hypertension, and more particularly to the treatment of hypertension in individuals following intrauterine programming of cardiovascular pathophysiology.

BACKGROUND

It is known that disordered fetal growth which is caused by many events including maternal undernutrition during pregnancy, as well as having immediate effects on the fetus, may have long term health consequences for individuals (Barker, D.J. Outcome of low birthweight, *Hormone Research* 42:223-230, 1994; Barker, D.J. Growth in utero and coronary heart disease, *Nutr Rev.*, 52:S1-S7, 1996). In particular, it has become evident that in addition to the well recognised long term sequelae of persistent growth failure, disordered fetal growth is associated with a higher incidence of hypertension, cardiovascular, cerebrovascular and metabolic disorders in adulthood. (Barker, D.J. Outcome of low birthweight, *Hormone Research* 42:223-230, 1994; Barker, D.J. Growth in utero and coronary heart disease, *Nutr Rev.*, 52:S1-S7, 1996; Woodall, S.M., *et al.*, Chronic Maternal Undernutrition in the Rat Leads to Delayed Postnatal Growth and Elevated Blood Pressure in Offspring, *Pediatr. Res.* 40: 438-443, 1996).

Hypertension, or high blood pressure, is a particularly significant problem in the adult population. This is because it is common, its consequences are far reaching and can be devastating and the symptoms do not show until late in its course. High blood pressure is one of the major risk factors for coronary heart disease and strokes. It can also lead to congestive heart failure, aortic dissection, and renal failure. Over half of patients with angina pectoris, sudden death, stroke, and atherothrombotic occlusion of the abdominal aorta or its branches have hypertension. Greater than 70% of people with dissecting aortic aneurysm, intracerebral haemorrhage, or rupture of the myocardial wall have high blood

pressure. It is a major risk factor for atherosclerosis. Treatment of high blood pressure can prolong life. Screening programmes reveal that 25% of the general population are hypertensive (Schoen, F.J. (1994). Blood Vessels. In Robbins Pathologic Basis of Disease. Edited by R.S. Cotran, V. Kumar, and F.J. Schoen. Philadelphia: W.B. Saunders Company. 467-516). The prevalence of high blood pressure increases with age. However, in older age groups the disease is usually relatively mild compared to that in young adults where it is often more severe. Approximately 90 to 95% of hypertension is idiopathic and of the remaining 5 to 10%, most is secondary to renal disease. Both primary and secondary hypertension may be either benign or malignant.

In the majority of cases, hypertension remains at a modest level and fairly stable from years to decades. However, if the raised blood pressure is not controlled by anti-hypertensive agents, it frequently causes disability and death from heart failure, and substantially increases the risk of myocardial infarction and strokes. Approximately 5% of people have malignant hypertension where blood pressure rapidly increases and if left untreated, leads to death in one to two years.

Recognising the significance of the problem, it is an object of the present invention to provide a method of treating hypertension, in at least a subset of the population (individuals which experienced intrauterine undernutrition or growth retardation or an adverse postnatal environment), or at least to offer the public a useful choice.

SUMMARY OF THE INVENTION

Accordingly, in a first aspect the present invention provides a method of treating hypertension in a mammal, which has experienced intrauterine under nutrition and/or growth retardation or an adverse post-natal environment, the method comprising the step of administering to the mammal an effective amount of an

agent, wherein the agent is a ligand which binds to, and activates, the growth hormone receptor.

In another aspect, the present invention provides a method of treating hypertension in a mammal, which has experienced intrauterine under nutrition and/or growth retardation or an adverse post-natal environment, the method comprising the step of administering to the mammal an effective amount of growth hormone, an analog thereof, or a functionally equivalent ligand.

Generally, the hypertensive state of the mammal will be the result of intrauterine fetal programming, or of an unfavorable/adverse postnatal environment (eg. a hypercaloric diet). However, any mammal with hypertension can be treated in accordance with the above methods.

Preferably, the mammal to be treated is an adult mammal.

As used herein, the term "intrauterine undernutrition or growth retardation" means disordered fetal growth with causes which include maternal undernutrition, placental insufficiency, endocrine abnormalities and substance abuse, as evidenced by a relatively low birth weight.

As used herein, "analog" means a protein which is a variant of growth hormone through insertion, deletion or substitution of one or more amino acids but which retains at least substantial functional equivalency.

The term "functionally equivalent ligand" means an agent which binds to and activates the receptors which growth hormone binds to and activates to give the anti-hypertensive effect.

In a further aspect, the invention provides a method of treating hypertension in a mammal, which has experienced intrauterine under nutrition and/or growth retardation or an adverse post-natal environment, the method comprising the step of increasing the effective concentration of growth hormone, an analog thereof or a functionally equivalent ligand in the mammal.

The method is particularly suitable for treating a mammal which has experienced either an adverse fetal environment, an adverse postnatal environment, or both.

Preferably, the effective concentration of said growth hormone analog or ligand is increased through direct administration.

Preferably, the effective concentration of growth hormone is increased through direct administration of growth hormone.

Alternatively, the effective concentration of growth hormone is increased through administration of an agent which either stimulates production of growth hormone or which lessens or prevents inhibition of growth hormone activity.

Preferably, the mammal is an adult human.

In a further aspect, the present invention provides the use of an agent selected from growth hormone, an analog thereof or a functionally equivalent ligand in the preparation of a medicament for treating hypertension in a mammal, which has experienced intrauterine under nutrition and/or growth retardation or an adverse post-natal environment.

In yet a further aspect, the invention provides the use, in the preparation of a medicament for treating hypertension in a mammal, which has experienced intrauterine under nutrition and/or growth retardation or an adverse post-natal

environment, of an agent which either stimulates production of growth hormone or which lessens or prevents inhibition of growth hormone activity.

Although the invention is broadly as defined above, it also includes embodiments of which the following description provides examples.

BRIEF DESCRIPTION OF THE DRAWINGS

In particular, the invention will be better understood with reference to the accompanying drawings, in which:

Figure 1 shows the mean systolic blood pressure in *ad-libitum* and developmentally programmed (DP) rat offspring. The data is mean ±SEM with a minimum of 5 animals per group; and

Figure 2 shows the percent change in systolic blood pressure in the rats following rbGH treatment for 21 days. The data is mean ±SEM, minimum of 5 animals per group.

DESCRIPTION OF THE INVENTION

The focus of the invention is on the treatment of hypertension. It is particularly on the treatment of hypertension in a subset of the adult population. The applicant's surprising finding, which underlies the present invention, is that administration of growth hormone to an adult mammal with hypertension can reduce systolic blood pressure. This is particularly true for mammals which have been subject as a fetus to adverse cardiovascular programming during pregnancy or which have undergone intrauterine growth retardation (IUGR), and have therefore been "programmed" to subsequently develop hypertension.

This finding with respect to growth hormone is unexpected given the previous reports associating an increase in systolic blood pressure with long-term exposure to endogenous growth hormone in acromegalics (Sacca, L., *et al.*, Growth Hormone and the Heart. Endocrine Reviews, Vol 15, No. 5, 555-573 [1994]) and low systolic blood pressure after a long-term lack of exposure to endogenous growth hormone in growth hormone deficient adults (Sacca, L., *et al.*, Growth Hormone and the Heart. Endocrine Reviews, Vol 15, No. 5, 555-573 [1994]). In other studies, growth hormone has been reported to decrease diastolic blood pressure (Johannsson, G., *et al.*, Growth hormone treatment of abdominally obese men reduces abdominal fat mass, improves glucose and lipoprotein metabolism and reduces diastolic blood pressure. *Journal of Clinical Endocrinology and Metabolism*, Vol 82, No. 3 727-734 (1997)), while having no effect on systolic pressure.

The invention therefore provides a method of treating hypertension in a mammal, such as a mammal which has experienced intrauterine growth retardation or under-nutrition or which has experienced a long term adverse postnatal environment such as hypocaloric or hypercaloric nutrition. It is however envisaged that the invention will have application in treating mammalian hypertension caused by other aetiologies, risk factors and environmental effects.

It is also envisaged that the principal application of the method of the invention will be to adult humans although treatment of pre-adult and non-human mammals is in no way excluded.

In a preferred aspect, the method of the present invention involves administering to the mammal an effective amount of growth hormone, an analog thereof or a functionally equivalent ligand. In a preferred embodiment, growth hormone itself is administered to the mammal.

The growth hormone can be any mammalian growth hormone, with examples being human growth hormone, bovine growth hormone, rat growth hormone and porcine growth hormone. It is however preferred that the growth hormone employed be human growth hormone where the mammal is a human.

The growth hormone which is used in this invention can be obtained from any commercial source.

In addition to growth hormone itself, the use of analogs of growth hormone or functionally equivalent ligands of growth hormone is contemplated.

A protein is a functional equivalent of another protein for a specific function if the equivalent protein is immunologically cross-reactive with, and has at least substantially the same function as, the original protein. The equivalent can be, for example, a fragment of the protein, a fusion of the protein with another protein or carrier, or a fusion of a fragment with additional amino acids. For example, it is possible to substitute amino acids in a sequence with equivalent amino acids using conventional techniques. Groups of amino acids normally held to be equivalent are:

(a) Ala, Ser, Thr, Pro, Gly;

(b) Asn, Asp, Glu, Gln;

[c] His, Arg, Lys;

(d) Met, Leu, Ile, Val; and

(e) Phe, Tyr, Trp.

It will also be appreciated that the present invention also extends to the administration of an agent which either stimulates production of growth hormone, or which lessens or prevents inhibition of growth hormone activity, ie to the administration of growth hormone agonists or secretagogues (substances which effect a direct increase in production of growth hormone).

Examples of agents which stimulate growth hormone and production or lessen or prevent its inhibition include growth hormone releasing peptides (GHRP) such as GHRP-1, GHRP-2, GHRP-6, hexarelin, G-7039, G-7502, L-692,429, L-692,585, L-163,191 or growth hormone releasing hormone (GHRH) or inhibitors of growth hormone antagonists (substances which bind growth hormone or otherwise prevent or reduce the action of growth homone within the body). These latter compounds exert an indirect effect on effective growth hormone concentrations through the removal of an inhibitory mechanism, and include substances such as somatostatin release inhibitory factor (SRIF).

The active agent can be administered using any suitable route. Where growth hormone is the active compound to be administered, it will generally be administered as an injectable formulation, in combination with one or more suitable carriers or excipients. Those persons skilled in the art will appreciate how suitable formulations can be prepared.

The active agent can also be administered in combination. For example, a combination of growth hormone and other conventional anti-hypertensive agent(s), for example ACE (angiotensin-converting enzyme) inhibitors such as quinapril, is also contemplated.

Another possibility is administration of a replicable vehicle encoding the growth hormone/analog/ligand to the patient. Such a vehicle (which may be a modified cell line or virus which expresses growth hormone/analog/ligand within the patient) could have application in increasing the concentration of the active compound within the patient for a prolonged period. Such a vehicle could well form part of an implant.

Dosage levels will be formulation dependent. However, by way of example, the recommended dosage rate of growth hormone formulated for injection would be in the range of 0.1ug/kg/day to 1mg/kg/day. A preferred dosage rate would be from approximately 2 to 200 ug/kg/day.

The invention will now be further described with reference to the following non-limiting examples.

EXAMPLES

Experimental

Virgin Wistar rats (age 100±5 days, n=15 per group) were time mated using a rat oestrous cycle monitor (Fine Science Tools INC., North Vancouver, BC, Canada) to assess the stage of oestrous of the animals prior to introducing the male. Day 1 of pregnancy was determined by the presence of spermatozoa after a vaginal smear. After confirmation of mating, rats were housed individually in standard rat cages containing wood shavings as bedding and with free access to water. All rats were kept in the same room with a constant temperature maintained at 25°C and a 12-h light:12-h darkness cycle. Dams were randomly assigned to receive food either *ad-libitum* (n=30, 15 study animals and 15 dams for crossfostering) or to receive 30% of *ad-libitum* (determined by measuring food intake on the previous day of an *ad-libitum* fed dam). The diet composition was protein 18%, fat 4%, fibre 3%, ash 7% and carbohydrate 58% (Diet 86, Skellerup Stock Foods, Auckland, New Zealand). Food intake and body weights were recorded daily.

Following birth, offspring from restricted fed dams were crossfostered onto *ad-libitum* fed mothers. Crossfostering is necessary due to lactational insufficiency in restricted fed dams. Litter size was adjusted to 8 pups per litter. Pre-weaning weights of all pups were recorded daily. At weaning (age 21 days) pups were sexed and housed in cages (males 2 per cage, females 3 per cage) and fed one of three diets regimes (normal, *hyper*caloric and *hypo*caloric (70% of normal)) *ad libitum* for the remainder of the study. At 90±5d (corresponding to adulthood), systolic blood pressure recordings were taken (n=12 per group).

Treatment was then commenced for 21 days with recombinant bovine growth hormone (rbGH) at a dose of 10ug/g/day given over 2 subcutaneous injections (8am and 5pm). Control animals were treated with carbonate buffered saline (CBS, pH 9.4) using an identical protocol. Immediately prior to sacrifice (24-48hrs), a repeated systolic blood pressure recording was taken using identical conditions (method is outlined below).

Normal and Hypercaloric Diets

Two custom made diets were prepared for the study. The composition of the diets was as follows:

Control diet:	protein 19.4%, fat 5%, fibre 5%, salt 1.5%, 2959 kcal/kg
Hypercaloric diet:	protein 30%, fat 30%, fibre 5%, salt 1.5%, 4846 kcal/kg

Both diets had a protein/energy ratio of 26%. Hypocalorically fed animals were given 70% of the intake of the DP control fed animals.

Methods

Systolic blood pressures were recorded by tail cuff plethysmography according to the manufacturer's instructions (Blood pressure analyser IITC, Life Science, Woodland Hills, CA, USA). Rats were restrained in a clear plastic tube in a heated room (25-28 °C). After the rats had acclimatised (10-15min) the cuff was placed on the tail and inflated to 240mmHg. Pulses were recorded during deflation at a rate of 3mmHg/sec and reappearance of a pulse was used to determine systolic blood pressure. A minimum of 3 clear systolic blood pressure recordings were taken per animal. Coefficient of variation for repeated measurements was <5%.

Results

Prior to onset of growth hormone therapy, developmentally programmed (DP) offspring showed a marked degree of hypertension as compared to *ad-libitum* offspring on a control diet ($p < 0.001$). Systolic blood pressure in DP offspring was further exacerbated by exposure to *either* a hypercaloric or hypocaloric diet postnatally ($p<0.001$, Figure 1).

Systolic blood pressure was significantly decreased in all DP animals treated with rbGH for 21 days (Figure 2). Although *ad-libitum* animals on a hypercaloric diet showed a significant increase in systolic blood pressure prior to treatment, growth hormone therapy did not reduce the degree of hypertension observed in these animals. Similarly, offspring from *ad-libitum* control fed mothers showed no significant change in systolic blood pressure following treatment. The reduction in systolic blood pressure was most marked in the DP animals fed hypocalorically. *Ad-libitum* and DP offspring treated with vehicle only showed no significant change in systolic blood pressure.

Conclusion

The above results clearly demonstrate the efficacy of growth hormone treatment in reducing systolic blood pressure in hypertensive animals whose hypertension is either caused by fetal programming or by an adverse postnatal environmental effect such as hypercaloric or hypocaloric nutrition. The very surprising finding of this example is that growth hormone did not reduce blood pressure in the normal control animals.

There are no examples in the literature where growth hormone has caused such a profound fall in systolic blood pressure in a hypertensive animal. Therefore the mechanisms of this effect either by effects on peripheral resistance of by direct action on the heart are unknown. The almost complete normalization of systolic blood pressure in these hypertensive animals is also a surprise.

INDUSTRIAL APPLICATION

Hypertension is a multi-faceted health problem of aging, genetics and, particularly, lifestyle. For example, the combination of post-natal diet and undernutrition causes health problems in terms of high blood pressure. However, the combination of undernutrition or another fetal insult plus cigarette smoking also causes hypertension. Therefore the "programming" plus a post-natal insult (such as hypercaloric or hypocaloric diet) will cause hypertension.

It is believed that the method of the present invention will be effective in treating hypertension, particularly in offspring following fetal intrauterine undernutrition or

growth retardation during pregnancy. The possibility of effective hormonal therapy for the hypertensive population is of immense public health significance.

Although the invention has been described with reference to a particular embodiment, it will be appreciated by those persons skilled in the art that variations and modifications may be made without departing from the spirit and scope of the invention.

CLAIMS

1. A method of treating hypertension in a mammal, which has experienced intrauterine under nutrition and/or growth retardation or an adverse post-natal environment, the method comprising the step of administering to the mammal an effective amount of an agent, wherein the agent is a ligand which binds to, and activates, the growth hormone receptor.

2. A method of treating hypertension in a mammal, which has experienced intrauterine under nutrition and/or growth retardation or an adverse post-natal environment, the method comprising the step of administering to the mammal an effective amount of an agent selected from the group consisting of growth hormone, an analog thereof, and a functionally equivalent ligand.

3. A method as claimed in either claim 1 or claim 2 wherein the mammal has experienced an adverse postnatal environment comprising a hypocaloric or hypercaloric diet.

4. A method as claimed in any one of claims 1 to 3 wherein the mammal is an adult mammal.

5. A method as claimed claim 4 wherein the mammal is an adult human.

6. A method as claimed in claim 5 wherein the agent administered to the mammal is growth hormone.

7. A method as claimed in any one of the preceding claims wherein the agent is administered to the mammal in combination with a second anti-hypertensive agent.

8. A method of treating hypertension in a mammal, which has experienced intrauterine under nutrition and/or growth retardation or an adverse post-natal environment, the method comprising the step of increasing the effective concentration of growth hormone, an analog thereof or a functionally equivalent ligand in the mammal.

9. A method as claimed in claim 8 wherein the mammal has experienced an adverse postnatal environment comprising a hypocaloric or hypercaloric diet.

10. A method as claimed in either claim 8 or claim 9 wherein the effective concentration of the growth hormone, an analog thereof or a functionally equivalent ligand is increased through administration of an agent which either stimulates production of growth hormone or which lessens or prevents inhibition of growth hormone activity.

11. A method as claimed in either claim 8 or claim 9 wherein the effective concentration of growth hormone is increased through direct administration of growth hormone.

12. A method as claimed in any one of claims 8 to 11 wherein the mammal is an adult human.

13. The use, in the preparation of a medicament for treating hypertension in a mammal, which has experienced intrauterine under nutrition and/or growth retardation or an adverse post-natal environment, of an agent selected from the group consisting of growth hormone, an analog thereof and a functionally equivalent ligand.

14. The use as claimed in claim 13 wherein the mammal has experienced an adverse postnatal environment comprising a hypocaloric or hypercaloric diet.

15. The use as claimed in either claim 13 or claim 14 wherein the medicament is for treating an adult human.

16. The use as claimed in any one of claims 13 to 15 wherein the agent is growth hormone.

17. The use as claimed in any one of claims 13 to 16 wherein the medicament is for administration in combination with a second anti-hypertensive agent.

18. The use, in the preparation of a medicament for treating hypertension in a mammal, which has experienced intrauterine under nutrition and/or growth retardation or an adverse post-natal environment, of an agent which either stimulates production of growth hormone or which lessens or prevents inhibition of growth hormone activity.

19. The use as claimed in claim 18 wherein the mammal is an adult human.

Figure 1

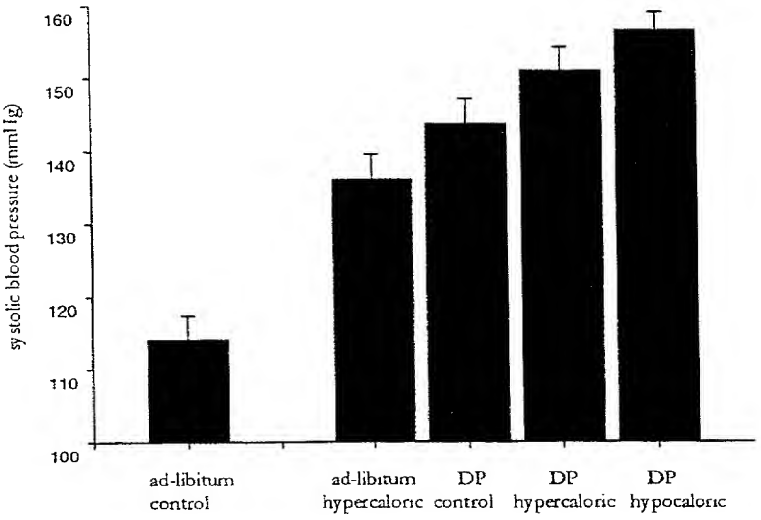
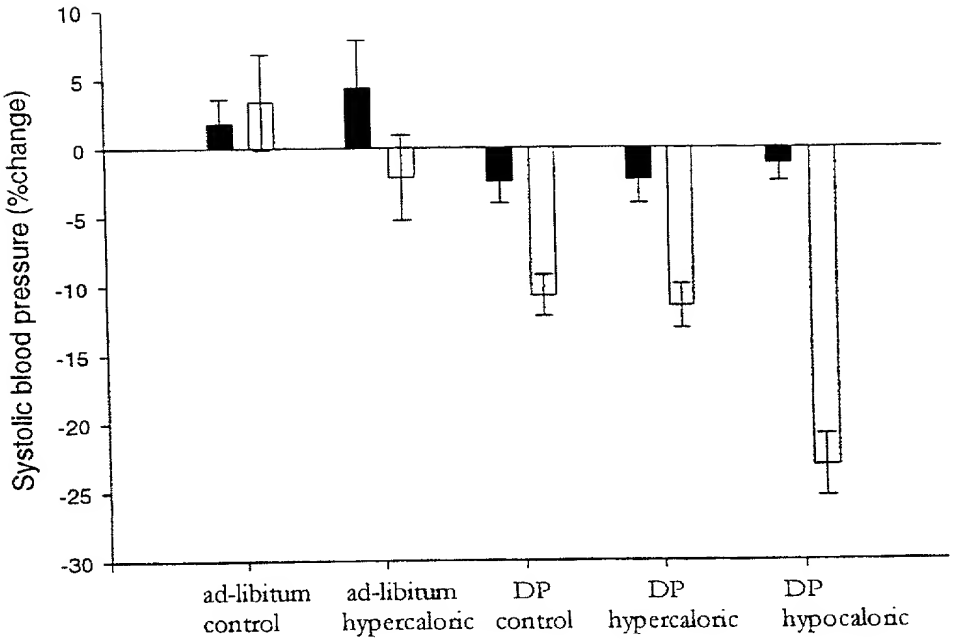

systolic blood pressure (mmHg)
160
150
140
130
120
110
100
ad-libitum control
ad-libitum hypercaloric
DP control
DP hypercaloric
DP hypocaloric

Figure 2


Systolic blood pressure (%change)
10
5
0
-5
-10
-15
-20
-25
-30
ad-libitum control
ad-libitum hypercaloric
DP control
DP hypercaloric
DP hypocaloric

#3

Nixon & Vanderhye P. C. (12/95)

RULE 63 (37 C.F.R. 1.63)
DECLARATION AND POWER OF ATTORNEY
FOR PATENT APPLICATION
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

As a below named inventor, I hereby declare that my residence, post office address and citizenship are as stated below next to my name, and I believe I am the original first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

TREATMENT OF HYPERTENSION

the specification of which (**check** applicable **box(s)**):

- ☐ is attached hereto
- ☐ was filed on _____ as U.S. Application Serial No. _____ **(Atty Dkt. No.).**
- ☒ was filed as PCT international application No. PCT/NZ99/00198 on 26 November 1999

and (if applicable to U.S. or PCT application) was amended on 5 February 2001

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above. I acknowledge the duty to disclose information which is material to the patentability of this application in accordance with 37 C.F.R. 1.56. I hereby claim foreign priority benefits under 35 U.S.C. 119/365 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed or, if no priority is claimed, before the filing date of this application:

Prior Foreign Application(s):

Application Number	**Country**	**Day/Month/Year Filed**
333035	New Zealand	26 Nov 1998

I hereby claim the benefit under 35 U.S.C. §119(e) of any United States provisional application(s) listed below.

Application Number	**Filing Date**

I hereby claim the benefit under 35 U.S.C. 120/365 of all prior United States and PCT international applications listed above or below and, insofar as the subject matter of each of the claims of this application is not disclosed in such prior applications in the manner provided by the first paragraph of 35 U.S.C. 112, I acknowledge the duty to disclose material information as defined in 37 C.F.R. 1.56 which occurred between the filing date of the prior applications and the national or PCT international filing date of this application:

Prior U.S./PCT Application(s): Application Serial No.	**Day/Month/Year Filed**	**Status: patented, pending, abandoned**

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon. And I hereby appoint **NIXON & VANDERHYE P.C., 1100 North Glebe Rd., 8th Floor, Arlington, VA 22201-4714, telephone number (703) 816-4000 (to whom all communications are to be directed),** and the following attorneys thereof (of the same address) individually and collectively my attorneys to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith and with the resulting patent: Arthur R. Crawford, 25327; Larry S. Nixon, 25640; Robert A. Vanderhye, 27076; James T. Hosmer, 30184; Robert W. Faris, 31352, Richard G. Besha, 22770; Mark E. Nusbaum, 32348; Michael J. Keenan, 32106; Bryan H. Davidson, 30251; Stanley C. Spooner, 27393; Leonard C. Mitchard, 29009; Duane M. Byers, 33363; Paul J. Henon, 33626; Jeffry H. Nelson, 30481; John R. Lastova, 33149; H. Warren Burnam, Jr., 29366; Thomas E. Byrne, 32205; Mary J. Wilson, 32955; J. Scott Davidson, 33489; Jerry D. Craig, 38026; Alan M. Kagen, 36178; William J. Griffin, 31260.

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FOR ADDITIONAL INVENTORS, check box ☐ **and attach sheet with same information and signature and date for each.**

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